I’m going to review some issues in the treatment research that we have right now, and as Boris alluded to, we were told very strictly to keep it to very few slides, so I’m going to be looking at recent trials, large scale randomized control trials for the most part. So if a trial isn’t up here it doesn’t mean it wasn’t done well, it just is we didn’t have space to put it in.

These are kind of exciting times for, for treatment research in pediatric bipolar disorder. We are certainly bipolar disorder itself is not as well studied as depression and schizophrenia and the adult world, and pediatric bipolar disorder is less so than adult bipolar disorder, but we are starting to get some interesting results from randomized controlled trials and we are going to look at some changes in pharmacotherapy and psychosocial interventions, especially in, in looking at the developments in pharmacotherapy with second generation antipsychotics, for FDA indications for mania. We are also going to look at some data about metabolic effects of second generation antipsychotics in children and adolescents. We’ll also look at some other studies looking at Depakote or Divalproex Sodium and a nice, some new data on comparing second generation antipsychotics Depakote and Lithium. And we’ll also look at a couple developments in psychosocial treatment of children and adolescents with bipolar disorder as well.

So this slide, and I adapted this from something from Bob Kowatch, so I have to thank him for it, and some additional information from Chris Correll is looking at a series of double blind placebo controlled trials of second generation antipsychotics in acute mania. These were all done in – as FDA registration trials and this just gives you the idea about the scope of how much work has been done.
And these are decent size sample sizes, so we are talking to hundreds to 200 to nearly 300 subjects. The age range tended to be 10 to 17, so this doesn’t necessarily apply to really young kids. These were short term acute treatment trials anywhere from 21 to 28 days, so we are talking 3 to 4 weeks. And the doses actually were pretty moderate, thinking about doses like Olanzapine and Marcio Tohen’s study were at 10 mg on average, Risperidone they used a low and high dose range, and that’s also the way the Aripiprazole and Quetiapine studies were done. And the Ziprasidone study kind of a mid-range dose. And one thing I think you’ll notice looking at this chart of – looking at placebo response, generally pretty low, 22%, 26%, 26%, 37%, 35%, so not real strong placebo response in these acute mania trials.

And the other thing I think that people remark on is actually the response rate, although not – you know we always want it to be higher, reasonably good, in the 50 to 60% range for the most part. And this is actually a pretty substantial effect size. If you want to look at something like a more continuous measure, like the Young Mania Rating Scale, for instance, you can also see big effect sizes here, so this is the average decrease with placebo for these drugs in the sort of pinkish, and then we have low dose and high dose changes and you can see big changes between – differences between placebo and active drug, both even at the low dose and the high dose. And these effect sizes are as big or bigger than the effect sizes of second generation antipsychotics in the acute mania trials of adults.
So exciting news and actually the results of these trials did lead to Aripiprazole, Quetiapine and Risperidone all getting indications for the treatment of acute mania in children and adolescents; however though the efficacy side shows exciting promise, unfortunately these medications do show some substantial metabolic effect – negative metabolic effects in kids, certainly in a proportion of kids. This is Christophe Correll’s terrific study in JAMA where he was looking at kids who were essentially antipsychotic naïve, so they weren’t taking anything. So it’s like you know you have the patient in your office, you have to decide what to do, not on anything else, what’s going to be the effect of this medicine when I, when I put this child on this medicine?

Looked over about a 3 month period, mean of about 14 weeks and looking at the mean weight gain, and we are talking some pretty substantial weight gain, Olanzapine over the 13 weeks, about 8.5 kilograms on average, 6.1 for Quetiapine, and the untreated, meaning kids that ended up refusing treatment not really substantial change. Now one thing that you do have to do when you are thinking about child studies, kids are growing taller too and you need to take that into consideration as you are looking at the impact of weight. However he also looked at BMI percentile, so where did they change sort of on you know relative to their peers as far as their weight for height ratio? And again, big changes, 24 points of BMI percentile, so somebody on average going from maybe a 60 percentile to 84. And that’s just in 14 weeks.

Also not as strong, but similar, similarly concerning changes for Quetiapine, Risperidone and Aripiprazole. From Christophe’s data I think you can get a pretty good sense that Olanzapine seems
to have a more impactful – has a greater impact on, on the – the weight gain and metabolic status here.

Looking at metabolic parameters after SGA treatment, you know some concerning issues, fasting blood glucose and cholesterol LDL and triglycerides, Olanzapine is significant increases in all of these over, over the period of time. The other SGAs scattered increases, so increased total cholesterol, triglycerides for Quetiapine, Risperidone just changes in triglycerides, change in LDL for Aripiprazole, and again the kids that were not treated did not have significant changes.

So putting this together I think we can say you know promising results for efficacy, somewhat concerning issues as far as metabolic status as was alluded to this morning into – in our morning plenary, this is an issue that we need to monitor. And probably preferentially not a huge difference at least in Christophe’s study among these three second generations but clearly Olanzapine a bit more of a problem and I think that’s one reason why the FDA actually said that it needs to be considered second line treatment for acute mania in kids.

Divalproex Extended Release, well proven efficacy in adults for acute mania or mixed state, well designed study by the company, Karen Wagner is the lead author on it. Unfortunately showing absolutely no difference between the kids who were on the Divalproex versus the placebo. Placebo response rate right in line with all of the other studies, about 23%, so there was nothing really unusual about this cohort compared to the second generation antipsychotic studies. The mean
concentrations at week 2, their target concentration 90, you know so it’s not underdosing, not necessarily overdosing as well. It was titrated to clinical response, so you know kids that didn’t respond could go up higher. And just absolutely no difference, you can’t get a more negative study than that unfortunately. So we have an idea about second generations being better placebo, Divalproex in this one study not being better than placebo, but that’s really not enough to make a decision. What would be nice is looking at some comparative results, and we have a couple of studies that have been able to do this.

Manny Pavuluri in this nice study that was published in the Bipolar Disorders Journal, 6 weeks treatment, blinded so that the children and parents didn’t know what the child was taking and used relatively conservative doses of Risperidone, about 1 ½ mg. Again Divalproex levels up in the 90s, showing that over the 6 weeks about a 78% response rate with the Risperidone versus 46% response rate with Divalproex. Significantly different, and especially sort of significantly different early on in treatment, it seemed like the Risperidone kids had sort of a more rapid response as well. So you know this is evidence that perhaps comparatively second generations may have better efficacy.

And now I’m going to tell you some very preliminary results, these haven’t been published yet. There are probably some tweaks that will happen overtime before it gets into press, but this is the Treatment of Early-Age Mania Study funded by the National Institute of Mental Health. It was a 5 site collaborative study, Children’s National Medical Center, Washington University, Texas Galveston, John’s Hopkins and Pittsburgh, we were fortunate to, to participate, that was looking at a
direct comparison of Risperidone, Lithium and Divalproex in kids with Bipolar 1 manic or mixed episode. So seeing how these drugs compete head to head.

The methodology, we are only look at – it’s a bit complicated but essentially kids could come in in a number of different states, either on or off medicine. We are going to actually look at just stratum 1, the kids that didn’t have exposure to any of the drugs prior to coming into the study and weren’t taking any medicines at the time. The study was kind of a hybrid of an effectiveness efficacy study, so you know the families and patients were not blind to the medication that they were taking, they knew they were going to get some medicine that we thought might be helpful; however the end point measures of efficacy and side effects were done by blinded raters who did not know what the, what the patient was taking. Unblinded clinicians adjusted the dose weekly based on clinical response and side effects, but we did have target blood levels for Lithium and Depakote to try to get up to at least initially.

Starting doses, just to give you a sense, was stratified by weight, so littlest kids got started on .25 of Risperidone, medium sized kids .5 and then a little bit more aggressive as you sort of – as it went on. Our initial target level was about .8 for Lithium and 75 for Divalproex, and then after that again titrated to clinical response and tolerability. Maximum doses 4 to 6 mg, we had if you didn’t respond and didn’t have side effects you could get up to a Lithium level between 1.1 and 1.3, and our top Divalproex level was 125. At the end point, meaning at the time that the child stopped the study either at 8 weeks or if they dropped out earlier, these were doses and levels that people were taking,
although I have to say that this wasn’t the typical level of the kids. On average earlier in the study they were at lower levels and this reflects in some ways the, the lack of efficacy.

And here is the basic results, and you know couldn’t get much clearer, big difference between Risperidone, 66% response rate. Two-thirds of the kids on Risperidone had a CGI, Clinical Global Impression scale of much or very much improved after the 8 weeks, whereas about a third of the kids on Lithium and only 25, or about a quarter of the kids on Divalproex. The difference between Lithium and Divalproex were not significant, we cannot say, can’t make a judgment about whether there is any difference in efficacy between these two drugs, but very clearly the Risperidone better than Lithium, better than Divalproex.

There was an issue I think about tolerability advantages with the Risperidone. Risperidone, actually fewer kids discontinued prior to the 8 week end point on Risperidone while fully a third of the kids on Lithium discontinued earlier. The Risperidone was more frequent discontinuation than the Lithium, not quite significant with the Divalproex. I will say it took heroic efforts to keep nearly – over 70% of these kids in the study for 8 weeks because these were outpatients with acute manic symptoms. And so it was you know a lot of work on the clinician’s part to keep things going.

You know given the sort of differences of rates of discontinuation, we did a preliminary analysis seeing if perhaps there was side effects that were different or reasons why people dropped that were different among the different types of medicine, and although the overall rates were different no one
type of problem stood out among the drugs, so it wasn’t like Lithium for instance had way more side
effects and discontinuation due to side effects than the Risperidone. It was more cumulatively on
average they just discontinued more, and you could see about 5% psychiatric hospitalization there.

So what about tolerability and metabolic effects? Clearly weight gain was greater on the
Risperidone, 3.3 kg on average over the 8 weeks. There was some weight gain on the Lithium and
Depakote, but not nearly as much. Surprisingly enough, although this I’d have to say a significant
difference in how this study was done, the lipids and glucose measurements were not fasting in the
TEAM study and that’s different than Christophe Correll’s study. We did not see an impact on lipids
on the kids on Risperidone, but again this was nonfasting. As far as other laboratory test changes,
clear increase in prolactin with the kids with Risperidone, the clinical significance of this is a little
bit unclear because there is some data, Bob Finling has some data showing that oftentimes after an
acute increase in prolactin kids on Risperidone can decrease to close to the normal over time. So this,
we know there’s an acute change, we don’t know the long term implications of that. And also acute
increase in thyroid stimulating hormone, and on average kids were right on the border of being
considered hypothyroid at least by TSH criteria. Again, this is acute treatment, long term
implications of it unclear from this study. And this just gives you a sense of, as we were mentioning,
BMI Z-score sort of looking at it compared to their peers is probably the best way to, to look at the
effect of weight gain. You can see the Risperidone kids pretty much just kept going up as they stayed
in the study, whereas the Lithium and Divalproex kids had a little bit of increase but not
substantially.
So that sort of summarizes our medication information from the past couple of years. Let’s move quickly to some brief information about psychosocial treatments. Really nice study done by Mary Fristad looking at children ages 8 to 12, where it’s very hard to figure out how to handle these kids and, and what you can do to help. And she designed with her colleagues a multifamily psychoeducational psychotherapy program. Most of these kids that were in the study had bipolar spectrum, the rest had recurrent major depressive disorder. And this was really nice because it was an add-on treatment paradigm, this is you know adding onto whatever these folks were getting, so real nice sort of effectiveness component to it. They all were continued to keep using their continued treatments as usual, it wasn’t an incredibly intense treatment, 8 sessions. They did a separate child and parent group, so they took them together, brought them to the same place then separated them in different groups. The child component I know had sort of a play and action component to it as well. And they compared the kids that had the active intervention to kids on a wait list control group, you can see this was published in the Archives. The kids that were getting active treatment substantially decreased mood symptoms compared to the kids on the wait list control who had some, but not very much change in the, in their improvement in mood symptoms.

And then last off just a, a brief look at potential moderators to treatment response. We have a lot of different options for treatments, one thing that would be great is if we could look at a particular child or family situation and have a good idea about what treatment we should try first. You know could we try individual therapy, family therapy, group therapy? Is there something that can be a predictor
ahead of time that could guide us on what’s going to be the most successful? And this is some work that David Miklowitz and I had a chance to do, looking at our R21 Pilot Study in Family-Focused Therapy. And one thing that’s we were especially interested in was the concept of expressed emotion, either high over-involvement, emotional expression or high criticism. And David had designed the program really to sort of work on decreasing the expressed emotion over time, and that was a big sort of target of the, of the treatment. So reasonably he hypothesized you know if would high EE families benefit from the treatment more than low EE families? And that’s pretty much what we found, small study so you know has to be replicated but essentially the kids who had – that were in the high EE emotional expression, big improvements in depression and mania relative to the kids that didn’t get the FFT, so big differences in improvement, depression, mania, effect sizes of .5 to .6.

No difference in the low EE kids between enhanced care and family-focused therapy. Interestingly enough, actually the kids in low EE did better not getting the family-focused therapy at least in regards to their manic symptoms. Again, small study, we need to do some replications. We have a 3 site randomized control trial that will hopefully be able to look at the robustness of these results.

So in summary, I think that you know recent trends that we can take home, second generation antipsychotics are efficacious for the treatment of acute mania in youth, they may be more effective than Divalproex, possibly more than Lithium, but I don’t think one study is enough to make that kind of decision. Second generation antipsychotics have significant effects on metabolism and weight,
certainly there is a huge amount of needs. We need long term studies, we need to look at Lithium versus placebo, there is an NIMH, I’m sorry, NICHD study underway right now to do that. We have very little information on treatment of depression, and as Dr. Birmaher also mentioned, a lot of these kids come with subthreshold symptoms that are significantly impairing, and we don’t have any treatment trials of that.

Another couple of interesting things, psychosocial treatments may be effective for use with bipolar disorder. I think it’s really important to say that you know if you do something that’s non-medication it can be good adjunctive treatment. And the certain type of psychosocial interventions may work better for certain patients or patients with specific characteristics and certainly we have to work a little bit more on that, but that’s an exciting trend. And with that, I’m going to stop.